



2004

REPORT

CHIP
COPENHAGEN HIV PROGRAMME

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CHIP

COPENHAGEN HIV PROGRAMME

Copenhagen HIV Programme (CHIP) is an academic research unit. The continued aim of CHIP is the execution of front-line HIV-research. Therefore, we will continue to strengthen our network of collaborating partners, and remain focused on addressing clinically relevant questions that improves patient care.



Section 4

A. Ongoing

1. ...
2. ...
3. Dyslipidemia

B. Prior cardiovascular

C. History of depression

D. History of psychosis

E. Liver disease

1. Chronic elevation of liver transaminases
2. Chronic HBV infection
3. Chronic HCV infection
4. HDV infection
5. History of previous liver decompensation
6. Clinical signs of liver failure in the 4 weeks before death
7. Liver histology available (ever)

If Yes, please indicate:
the date of most recent biopsy

(dd-mm-yy eg 01-FEB-05)

the stage of fibrosis (0-4):



2004

2004 IN RETROSPECT

2004 was a year of consolidation and yet a year where a variety of new initiatives were made both within CHIP and to strengthen our methodologies and collaborative network of clinics across the globe.

The five main studies, EuroSIDA, D:A:D, ESPRIT, SILCAAT and SMART progressed as planned. Especially the “rescue” of the SILCAAT trial and the start (up) of the SMART study have required significant investment of personal resources. Additionally, the INITIO trial was completed in 2004. The group co-authored a total of 28 papers. 23 of the papers had a cumulative impact factor of 129 compared with 157, 77 and 124 in the three previous years. Two academic titles were successfully defended at the University of Copenhagen.

One of the main research efforts of CHIP is to coordinate large-scale, international observational studies of HIV-infected persons. It is critical to advance the methodology used for this type of research.

CHIP contributed with two initiatives in this respect in 2004. The “HIV Collaboration Data Exchange Protocol” (HICDEP) (p.22) format was updated and announced in Antiviral Therapy. This protocol is gaining importance as the main tool used in interstudy collaborations across the globe. We also took the initiative of standardizing the format and coding of data related to causes of death in HIV – the CoDe project (p.20). A large group of international experts met in Copenhagen in July 2004 to start this process. CHIP continues to coordinate this effort, which is expected to be the standard globally.

CHIP contributed to a course organized by the WHO to strengthen the infrastructure of capturing data on adverse events associated with antiretroviral therapy in 8 countries in the southern part of Africa.

Organizationally, CHIP became a freestanding research unit at the University Hospital of Hvidovre as of 1st of September 2004.

**FUTURE
PERSPECTIVES
AND CHALLENGES**

Scientifically

Continued focus on maintaining a healthy atmosphere of collaboration in the ongoing studies will remain important to CHIP. A large effort continues to be required to move the SILCAAT study forward, and an additional 600+ persons will hopefully be recruited from our region into SMART in 2005.

We will work hard to further understand the extent and mechanisms explaining the association between exposure to antiretroviral therapy and the gradually increased risk of cardiovascular disease. Liver disease is of major ongoing concern to the health of HIV-infected persons. Co-infection with hepatitis virus B & C is already known as a contributing factor. However, antiretroviral therapy may also accelerate the progression of liver disease, although solid data to demonstrate such an association is still missing. This will also be a research focus in 2005.

HIV-infected persons with access to antiretroviral therapy continue to die, although the fatality rate is substantially reduced and causes are more diversified compared to the era prior to the introduction of antiretroviral therapy. The CoDE project (p.20) will allow us to improve our understanding of causes responsible for the observed deaths. An interesting spin-off of this line of research is emerging data suggesting that the level of immunodeficiency seen in HIV may lead to an accelerated course of diseases not yet believed to be influenced by immunodeficiency, such as liver disease and non-AIDS defining cancers. If confirmed, this data could suggest that the benefits of antiretroviral therapy and other interventions aimed at improving the immune function may prove to be even more beneficial than what is current thought to be the case. More clarity on these findings will hopefully emerge in 2005.



Geographical disparity

A large diversity exists in the prognosis of HIV-infected persons between the continents, but this is also true even within Europe. A rapidly growing epidemic in Eastern Europe coupled with major shortcomings in provided adequate medical care of the affected population and a high rate of multi-drug resistant tuberculosis in the background population makes Eastern Europe extremely vulnerable in the coming years. CHIP has collaborated with colleagues from this region during the last 6 years and is dedicated to continue to focus a major part of our research efforts there. We strongly believe that clinical research is a major vehicle to improve the situation. However, in order to revert the situation, political leadership and substantial funding to strengthen the medical infrastructure are required.

In 2005, we will also initiate collaboration with the WHO in order to establish observational studies in the developing world on persons starting antiretroviral therapy. The know-how we have acquired in the last 10 years of implementing EuroSIDA across Europe can now be used in other continents that are in desperate need of acquiring data to guide a rational introduction of antiretroviral therapy in this region so severely affected by the HIV epidemic.

Funding

CHIP is entirely dependent on external project-specific funding. Since most of our major projects are up for refunding in 2005, a large bulk of work will focus on writing applications and subsequently secure the funds that will hopefully be the result of this exercise.

An application to the European Commission requesting continued support to EuroSIDA until 2009 was submitted in November 2004 and we should know the outcome hereof in April 2005.

Funding for D:A:D was recently renewed until 2006 and hopefully it will be possible in 2005 to secure funding for this study for an additional couple of years.

CHIP will be part of the leadership application to National Institutes of Allergy and Infectious Diseases in the USA to establish a global HIV trial network (the INSIGHT network) and will additionally submit a site application to cover related infra-structure cost.

The applications will be submitted in May and July and the outcome hopefully known before the end of the year. This is an extraordinarily exciting chance for CHIP to become part of such a monumental initiative.

Infrastructure

Due to the continued expansion and increased level of activity within CHIP in the last couple of years, the staff has suffered from an increasing lack of space. Additionally, new staff will be required in 2005. However, we have reliable fortunate indications to suggest that this situation will improve.

We will continue to focus on recruiting dedicated persons able and willing to engage fully in the ongoing activities, and at the same time contribute to the dynamic and academic atmosphere that currently exists within the group.

FINANCIAL CONTRIBUTORS

Study	Public	Private
Initio	Medical Research Council, UK	
EuroSIDA	EU Commision Swiss Federal Office for Education and Science	Boehringer Ingelheim, Bristol-Meyers, GlaxoSmithKline, Roche
DAD	The Oversight Committee for The Evaluation of Metabolic Complications of HAART. EMEA, FDA	Abbott, Agouron, Boehringer Ingelheim, Bristol-Myers, Glaxo SmithKline, Merck, Pfizer, Roche
Esprit	Nat. Inst. of Allergy & Infectious Diseases, NIH, US	
SILCAAT	Nat. Inst. of Allergy & Infectious Diseases, NIH, US	
SMART	Nat. Inst. of Allergy & Infectious Diseases, NIH, US	
ALCAR		Bristol-Meyers, Sigma Tau
BI Switch		Boehringer Ingelheim
NRTI Sparing		Abbott

OBSERVATIONAL STUDIES

D:A:D

Scientific purpose

The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) is a prospective multi-cohort study of HIV-infected persons under active follow up. The purpose of the study is to assess the incidence of myocardial infarction and other cardiovascular disease endpoints in HIV-infected persons, and to investigate whether treatment with antiretroviral drugs is associated with development of cardiovascular disease as a late onset adverse effect.

Description

11 cohorts worldwide are participating, with a total current enrolment of more than 35,000 patients from 188 clinics in 21 countries in Europe, USA and Australia. The patients have contributed more than 75,000 person-years of follow-up as of February 1st 2004. The original study population of 23, 441 were enrolled December 1999 - April 2001, and is referred to as D:A:D Cohort I; an additional 12,900 were enrolled in D:A:D Cohort II throughout the spring of 2004.

On average, patients are seen in the clinics every 3 months, and specific data collection for D:A:D takes place at least every 8 months. Each cohort gathers and computerises its data; subsequently it is merged in a database in Copenhagen.

Organisation

The coordinating office at CHIP is staffed by the principal investigator, the study coordinator and the central data-manager. It has the overall responsibility, including the coordination, collection and cleaning of data, review and query of events, and the preparation of draft research papers.

The coordinating office organises Steering Committee (SC) meetings with representation from each cohort, a lead statistician, EMEA, the patient community and the industry. The SC approves all analytic proposals prior to their execution and has the overall responsibility for the scientific conduct of the study.

Results

In 2004, the study presented data on changes in systolic and diastolic blood pressure and of occurrence of hypertension in HIV-infected individuals. This project found that elevated blood pressure in HIV-infected persons was associated with established risk factors for hypertension. Antiretroviral drugs had no independent harmful effect on blood pressure changes or the development of hypertension.

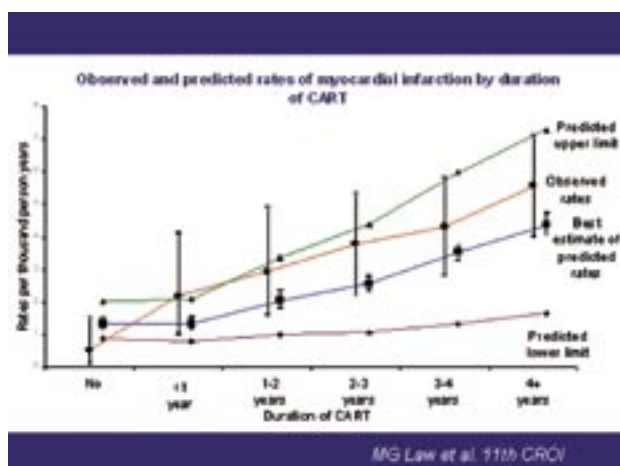
Comparison of predicted versus observed rates of MI were also studied using the Framingham equation to predict the rate of MI, and compared these rates to the ones observed. These analyses showed that the observed rate of MI in the D:A:D Study was of a similar magnitude to, or slightly higher than, that predicted by the Framingham risk equation. Even though the primary analyses does not entirely explain the association, the fact that rates of MI and duration of cART increased in parallel, suggest that this may be explained through cART-induced changes in conventional CVD risk factors.

An analysis of whether the association of cART use and the risk of cardiovascular disease was similar when including other cardio- and cerebrovascular disease events, found that the cART association with a composite endpoint was very comparable with how cART affects the risk of MI. This finding is consistent with the hypothesis that atherosclerosis is a side effect of cART.

Future

The study is projected to continue at least until 2006, and provide more than 130,000 person-years of data.

The D:A:D Study continues to follow patients prospectively, focusing on the monitoring of the risk of cardiovascular disease and the association with more extended exposure to cART. The central research question to be solved in the future is which mechanisms that are explaining the associated risk of MI with combination antiretroviral therapy. Furthermore, the study is in a position to address predictors and trends of causes of death, and has broadened its scope by implementing a standardized coding from the CoDe Project (p. 20).





Scientific purpose

The main objective of the study is to follow the long-term clinical prognosis for the general population of HIV-infected patients living in Europe and to assess the impact of antiretroviral drugs on the outcome.

Description

EuroSIDA was initiated in 1994 and is sponsored by the European Commission. Additional support is given to the project through unrestricted research grants from GlaxoSmithKline, Roche, Boehringer-Ingelheim and Bristol-Myers Squibb. The study is headed by a 12-member steering committee, elected by the EuroSIDA investigators. CHIP is the coordinating centre.

EuroSIDA is the largest pan-European cohort study, and few studies of a comparable design are available on a global scale. As of December 31 2004, the study included 11,243 patients at 80 clinics in 29 European countries and Argentina. The latest enrolment wave was successfully completed in spring 2004 (cohort VI, 1,421 patients) and as a result, we now have 1,551 patients under follow-up at 20 HIV clinics in Eastern Europe. A total of 48,836 person-years of follow-up has been collected in the study and there are now 214,924 CD4 cell measu-

rements and 172,274 viral loads in the database. As of December 31 2004, a total of 36,772 plasma samples have been registered in the central plasma repository. The vast majority of sites in EuroSIDA contribute to the central repository and the collection of plasma samples is a mandatory part of the more recent cohorts.



The EuroSIDA plasma repository enables virological analyses by correlating the extensive clinical database with resistance data. The sequencing of plasma samples identified for specific projects

was carried out in 2004 by two EuroSIDA virological laboratories in London, UK, and Badalona, Spain. The establishment of a virological Think Tank consisting of virological experts from across Europe and headed by Lidia Ruiz from Badalona has further strengthened the virology portion of EuroSIDA. The purpose of the Think Tank is to generate proposals for new virological projects. Several projects on resistance have been advanced during 2004 and the first manuscript based on these efforts was published in *Antiviral Therapy* in October 2004. In addition, presentations on other virological projects have been made at international conferences.

Results

A total of 13 articles have been published in peer-reviewed journals in 2004 (see publication list on p. 32) with an additional 3 accepted for publication. There has been 55 articles published in peer-reviewed journals since 1997 directly emanating from the EuroSIDA study. The articles from 2004 cover topics such as: treatment failure and discontinuation; influence of prior therapy before starting combination therapy; effect of combination therapy on individual AIDS diseases; and, initial results from the virology group and the hepatitis group.

The EuroSIDA study has participated in and initiated international inter-cohort collaborations to address issues which cannot readily be answered within the EuroSIDA study itself. Such collaborations include the D:A:D study, the ART Cohort Collaboration, and the PLATO collaboration. These collaborations have been very fruitful in 2004 and are likely to be even more important in the coming years.

Finally, EuroSIDA presented eight abstracts at the major international HIV conferences in 2004 covering a variety of topics dealing with the key issues mentioned below.

The future

The key issues to be addressed within the EuroSIDA study in the coming years are:

- I) Hepatitis B and C co-infection
- II) Association between virological resistance and virological/immunological/clinical outcome.
- III) The epidemic in the eastern part of Europe
- IV) Long-term and rare toxicity of antiretroviral therapy

In 2005, we plan to include 2,500 new patients into the study (cohort VII), of which 1,250 are to be included at existing and new clinics in Eastern Europe. As follow-up accumulates, this will allow for more detailed analyses of issues especially relevant for Eastern Europe. (see article on CHIP and Eastern Europe on p. 21).

An application for funding was submitted to the European Commission in November 2004 to continue the work of EuroSIDA in the coming years (2005-2009). A decision is expected in April 2005.

The foundation for EuroSIDA remains the data provided by the 80 participating clinics. Over the last 10 years, many dedicated people have completed follow-up forms in a timely and accurate manner to allow the study to provide updated information on clinical practice in HIV clinics in Europe. The rate of lost-to-follow-up continues to be very low – less than 5% per year.

In addition to the high data quality, the active participation of many EuroSIDA investigators in specific scientific projects is another cornerstone of the study, making this multi-national cohort study a true team effort of European clinicians.

RANDOMISED CLINICAL TRIALS



Scientific purpose

SMART (A Large, Simple Trial Comparing Two Strategies for Management of Anti-Retroviral Therapy) is the most ambitious trial in terms of size and magnitude of follow-up information collected to have ever been conducted in HIV clinical research.

The purpose of this study is to compare the long-term clinical consequences of two strategies of antiretroviral management:

1. The virological suppression strategy which aims at continued use of antiretroviral therapy.
2. The drug conservation strategy which aims at minimising exposure to antiretroviral therapy as much as possible while maintaining a reasonable immune function.

The outcome to be compared between the two strategies is the risk of developing AIDS or death.

Description

The study is a randomised, multi-centre study, where a total of 6,000 patients will be enrolled from more than 300 sites in 30 countries.

CHIP serves as one of four regional coordinating offices for the implementation of the protocol across Europe and plan to include approx. 900 patients.

Results

The study is in its enrolment phase, 131 patients have been enrolled in our region, and 2,550 patients worldwide, at the end of 2004.

Sites in Austria, Belgium, Denmark, Finland, Germany, Norway, Poland, Portugal and Spain are already established and recruiting patients, and several new sites are on their way.

CHIP are making special efforts to include sites from all parts of Europe, with particular emphasis on countries from the eastern part of Europe, that has not previously participated in large scale studies. Interested sites in Russia, Lithuania, Rumania and Estonia have been identified and everything possible is being done to have these sites approved and included in the study.

The future

The recruitment continues throughout 2005, and is expected to be completed by the first of quarter of 2006, with an estimated 6,000 patients, from more than 300 sites in 30 countries, included at that time. The study will finish when the required 910 primary events have occurred, estimated at approx. 6 years after recruitment is complete.



Scientific purpose

The INITIO trial aims to evaluate three strategic approaches to combinations of antiretroviral drugs in sequence to sustain viral suppression and delay disease progression in ART-naïve persons.

1. ddl, d4T plus efavirenz (with a change to AZT, 3TC, abacavir plus nelfinavir if the treatment failed)
2. ddl, d4T plus nelfinavir (with a change to AZT, 3TC, abacavir plus efavirenz if the treatment failed)
3. ddl, d4T, efavirenz plus nelfinavir (with a change to a new treatment decided by the treating physician if the treatment failed)

Description

Initio is a multi-centre, open, randomised study with 915 individuals from 17 countries across Europe, Australia, New Zealand, Canada and Brazil that were joining the trial between February 1999 and April 2002. The average time participants had spent in the trial was just over 3 1/2 years when follow-up was closed in June 2004.

Results

In all three arms of the trial, a pronounced decline in level of HIV-RNA was observed, paralleled with an increase in immune status determined by level of CD4+ lymphocytes. However, at three years, arm # 1 has a 12% higher rate of viral suppression than arms # 2 and 3, whereas there were no difference between arms # 2 and 3 in rate of viral suppression. Furthermore, by June 2004, more persons allocated to arm # 1 were still on the allocated first drug combination than the other two groups. Conversely, there were no differences in immunological response and the three strategies also had comparable risks of clinical disease progression.

Hence, although the general response to HIV treatment was very good in all three arms of the trial the results show that when using ddl and d4T it is better to start HIV treatment by including efavirenz rather than nelfinavir or both efavirenz and nelfinavir. The results do not support the idea that HIV treatment should be started with more than 3-drugs in combination. It remains unknown whether similar results would be expected using different HIV drugs.

ROYAL FREE HOSPITAL (RFH) STUDIES

CHIP has a long-standing working relationship with the HIV clinic and the statistical department at the Royal Free Hospital (RFH), London. This collaboration continued through 2004 and currently includes 3 clinical trials which are all in agreement with the overall purpose of CHIP: to perform clinically relevant HIV research.

ALCAR

Scientific purpose

One important condition in HIV is the development of Distal Symmetric Poly neuropathy (DSP), which may either be caused by the infection itself, the treatment or a combination hereof. The purpose of ALCAR is to evaluate the safety and efficacy of acetyl L-carnitine (ALCAR) over 48 weeks in combination with antiretroviral therapy for the prevention of DSP and lipid abnormalities in treatment naïve individuals.

Description

ALCAR is a randomised, double blind, placebo controlled pilot study performed at two sites (London and Vienna). The role of CHIP in ALCAR is primarily that of contributing to the protocol development, implementation and coordination of the trial.

Results and the future

The trial has recruited 38 of an expected 50 patients and the enrolment period has been prolonged to the first half of 2005. The trial is expected to finish mid 2006.

BI SWITCH

Scientific purpose

All drugs can result in toxicities, however, these may vary even within the same class of drugs. The purpose of BI Switch is to assess the effects of changing from one drug (efavirenz) in one drug class (non-nucleoside reverse transcriptase inhibitors) to another drug in the same drug class (nevirapine). HIV-1 infected persons receiving HAART, with viral load < 50 copies/ml and experiencing CNS toxicity are eligible to participate. The follow-up period is 24 weeks.

Description

BI Switch is a randomised, open-label, single centre (London) pilot study. The role of CHIP in BI Switch is primarily contribution to the protocol development, implementation and coordination of the trial.

Results and the future

The trial has recruited 26 patients and enrolment will continue until 30 patients are available for analysis. 21 of the patients have already finished the study.

NRTI SPARING

Scientific purpose

All drugs can result in toxicities, but these vary between drugs and drug classes. Similarly, the potency of drugs varies between drugs and drug classes. The current treatment guidelines recommend the use of three drugs from two drug classes as first-line treatment. However, this is partly based on data from trials using less potent drugs than newly marketed drugs. The NRTI sparing study will assess the efficacy, safety, tolerability and pharmacokinetics over 48 weeks, of a two-drug, two-class regimen (lopinavir/ritonavir plus nevirapine), excluding drugs from the most commonly used (and recommended) drug class (nucleoside reverse transcriptase inhibitors). Adult HIV-1 infected individuals, naïve to the study drugs and without any mutations in HIV-1 RNA to these drugs, are eligible to participate.

Description

NRTI sparing is an open-label pilot study, carried out at two sites in London (Royal Free and St. George's hospitals). The role of CHIP in the NRTI sparing study is primarily contribution to the protocol development, implementation and coordination of the trial.

Results and the future

The trial was opened for recruitment in autumn 2004. It has enrolled 4 patients and the enrolment period is expected to continue until the end of 2005. In total, 40 subjects will be recruited into the study.



Royal Free Hospital statistical group. Photo: Zoe Fox

INTERLEUKIN-2 STUDIES



Scientific purpose

Potent antiretroviral drug combinations have consistently been shown to result in prolonged survival and less HIV-associated morbidity. The target of these drugs is the suppression of the HIV replication. An additional strategy for the management of HIV could be to stimulate the recovery of the immune function. Two long-term, large-scale studies are currently investigating an immunological response by selectively raising the CD4+ lymphocyte count rather than targeting the virus. The studies investigate this approach by assessing the effects of subcutaneous recombinant interleukin-2 (sc rIL-2) and no sc rIL-2 on disease progression and death over a long-term follow-up period in patients who are taking combination antiretroviral drugs.

The following two studies were designed to investigate the effects of sc rIL-2 in patients with a continuum of low CD4+ lymphocyte counts (the SILCAAT study) and medium to high CD4+ lymphocyte counts (the Esprit study).

In the future a further study will investigate the use of sc rIL-2 on treatment naïve patients (the Stalwart study).

Preliminary results make it likely that IL-2 boosted combination therapy have a significant advantage over traditional therapy, but the future use of IL-2 as part of a standard therapy can only be determined when in-depth analysis of the ongoing studies have been completed.

Description

The study is a phase III, randomised, open-label, multi-centre study involving 255 sites in 25 countries on 6 continents - and with 4,150 patients recruited, it is the largest randomised study in HIV research to date.

CHIP is one of four Regional Coordinating Centres (RCCs) and coordinates the study specifically in Austria, Belgium, Germany, Poland, Portugal, Spain, and the Scandinavian countries with 982 patient under management.

Results and the future

Several Investigator Meetings have taken place throughout the year, at CROI, in Bangkok and in Glasgow (for Europeans Investigators). One of the main issues, especially discussed at the Bangkok meeting was the IL-2 cycling initiative, an effort to persuade patients in the IL-2 arm to continue using IL-2 at regular intervals. The main obstacle seems to be the sideeffects connected with the use of IL-2, but it should be possible to limit these. Further information concerning this subject will be gathered and the initiative will continue in 2005.

An article published in *Clinical Infectious Diseases* analysed results from the three Vanguard studies preceding the Esprit study and found that higher doses of sc IL-2 resulted in greater CD4 cell count changes, compared with a control group. These results were the basis for the sc IL-2 doses used in the Esprit study.



A poster comparing observed event rates and the projected event rates (based on the EuroSIDA study) in the Esprit study have been presented in Bangkok. These early data suggest that an average of 6-7 rather than 5 years of follow-up may be required to achieve the target of 320 primary events.

A Data Safety and Monitoring Board (DSMB) meeting took place in February. After reviewing safety and efficacy data from all sites the DSMB concluded that “no consideration of early stopping based on safety or efficacy is indicated.” The Esprit study will continue without change of conduct.

More than 1/3 of targeted endpoints have been observed up to the end of 2004, and patients will continue to be followed until a common closing date when 320 confirmed progressions of disease endpoints have been observed.

Description

The study is a phase III, randomised, open-label, multi-centre study involving 1,971 patients from 129 sites in 11 countries on 5 continents. Like in ESPRIT the role of CHIP in SILCAAT is to be one of four RCCs coordinating the sites in Belgium, Germany and Spain with 421 patients under management.

Results and the future

The transition of SILCAAT to the Esprit group is now completed, participating sites have been registered to the new version of the protocol whose data collection- and endpoint reporting are very similar to that of Esprit, and most patients participating in the study have re-consented to the new protocol version.

Joint Esprit/SILCAAT Investigator Meetings have taken place throughout the year, at CROI, in Bangkok and in Glasgow (for Europeans Investigators) and also a joint cycling initiative, as described under the Esprit study, has been undertaken.

SILCAAT was evaluated at DSMB meetings in February and October. The conclusions were the same as for Esprit that “no consideration of early stopping based on safety or efficacy is indicated.”

SILCAAT continues without change of conduct.

More than 1/3 of the necessary endpoints have been observed, and patients will continue to be followed until a common closing date when 300 confirmed progressions of disease endpoints have been observed.

ACKNOWLEDGEMENTS

The academic staff at CHIP is well recognized for their efforts by being named authors on scientific papers. However, CHIP could not function without the “group work” provided by the staff at the accounting section, clinical monitors, the administrative support staff, the technicians and datamanagers. Special thanks to Ms *Karoline Jensen*, Ms *Karen Skov Hansen*, Mr *Allen Sawitz* and Mr *David Mollerup*.

Some of our key staff left the group in 2004 to seek new challenges. Special thanks to Dr *Ulrik B. Dragsted*, and Ms *Michela Nielsen* for their long-term

dedication. Fortunately, we were able to attract new capable staff as their replacement.

The board of directors of CHIP continues to provide constructive guidance to ensure that the overall aim of why CHIP was started remains intact. The three external members of the board, Prof *Nils Brünner*, Prof *Hans Bisgaard* and Mr *Michael Nord* are acknowledged with appreciation.

AWARDS

The Wyeth award for clinical microbiology

The Danish Society for Clinical Microbiology selects an award-winner annually. On behalf of CHIP, *Jens Lundgren* received the 2004 version of this award at a ceremony at the State Serum Institute, November 2004.

The Justus Ström memorial lecture

In honor of one of the pioneers behind the creation of the infectious diseases specialty in Sweden, the Swedish Society for Infectious Diseases nominates a person to give this lecture. The 2004 Justus Ström memorial lecture “The battle to maintain health in HIV” was held by *Jens Lundgren* on behalf of CHIP at

the annual meeting of the Swedish Medicine Society, Gothenburg, November 2004.

HS and National Board of Science awards

Nina Friis Møller, MD, PhD has received funding from HS (Hospital cooperation of Copenhagen) and the National Board of Science, to continue research into cardiovascular sideeffects of antiretroviral treatment.

PROJECTS

THE CODE PROJECT

Scientific purpose

- 1) To develop an algorithm to classify deaths of HIV-infected persons.
- 2) To create a surveillance system for emerging trends in the causes of death based on the consensus algorithm.

Description

A significant proportion of deaths in HIV-1 infected persons is now caused by non-AIDS events. It is possible that deaths from diseases related to an accelerated aging process, coinfections or other comorbidities will become more frequent.

It is important to closely monitor the causes of death in this population in order to target interventions appropriately, should specific causes of death emerge or become predominant.

Furthermore, it is important to be able to evaluate the risk factors for such emerging diseases, including their possible relationship with immunodeficiency.

Until now there has not been a uniform classification system for causes of death in HIV patients. Studies have either created their own coding systems or have used ICD codes from death certificates. In many cases, the ICD system cannot be directly adapted to HIV infected persons. Many AIDS defining illnesses are poorly identified in the ICD system, and some diseases (e.g. CNS diseases) have a different aetiology in HIV patients and are therefore not covered by the ICD system, or at great risk of mis-classification. There has generally been a lack of standardization, and a central review process is rarely used. This has led to a wide variation in how the causes of death were coded and recorded, both within and between different studies.

Organization

In July 2004, a meeting was held in Copenhagen with the participation from executive committees of a large number of pivotal observational studies and clinical trials. It became clear that there was a need for a harmonization and standardization of the approach taken when data was collected on cause of death and these data were reviewed. As a result, the CoDe Project was initiated and a working group formed.

CHIP acts as coordinating office, and as a member of the working group, is part of the executive body of the CoDe project. At least once a year the group evaluate the progress and development as well as maintain the database specifications.

Pilot

Through 80 cases in an initial pilot phase, the CoDe Case Report Form, guidelines and the review process itself were tested by the CoDe working group and modified accordingly, to ensure clarity of the guidelines and to facilitate the collection of data.

CoDe methodology

Postmortem the attending physician fills out a CoDe CRF according to the guidelines. Subsequently, the CRF is evaluated by at least two reviewers and a specific coding of the cause(s) of death and its relationship to immunodeficiency is determined. The case is also classified with degree of certainty, intended to reduce the number of cases classified as unknown. The results are recorded on the reviewers form and sent for analysis.

Future

The CoDe methodology is publicly available and has so far been incorporated in the 11 cohorts in the D:A:D collaboration. Other studies are currently evaluating its use and whether to implement it as a standard.

THE EASTERN EUROPE PROJECT

Description

The HIV epidemic in Eastern Europe has developed dramatically within the last few years and differs in several aspects from the situation in Western Europe. In particular, a very large part of the HIV-infected patients in Eastern Europe are not receiving antiretroviral treatment and a majority of them are injection drug users.

The EuroSIDA Study has for several years been engaged in Eastern Europe: HIV-infected patients have been enrolled and followed at clinics in Poland, the Czech Republic and Hungary (since 1999) as well as at clinics in Estonia, Latvia, Lithuania, Romania, Slovakia, and the Ukraine (2001). This collaboration has been substantially expanded during the winter 2003/2004 by enrolling large numbers of patients from the already existing clinics as well as from new clinics in Russia, Belarus and Serbia-Montenegro. As of late 2004, 1,551 patients are being followed in 20 clinics across Eastern Europe, and the first results focusing on the situation in this region have already been presented in 2003 and 2004. As follow-up accumulates, more detailed analyses will focus on regional differences in access and use of antiretroviral therapy and the implication thereof on mortality and morbidity. In addition, we are currently in contact with other HIV-clinics in Eastern Europe and plan to include more than 2,000 new patients into EuroSIDA in 2005 and 2007. This effort will in particular involve new clinics in Russia (especially Moscow), Belarus, Bulgaria and the Ukraine.

It is the intention of CHIP to further develop the collaboration with HIV-clinicians in Eastern Europe using the EuroSIDA network as a platform. Where CHIP is a part of the international leadership we intend to involve HIV-clinics in Eastern Europe in existing and future randomised trials. Clinics in Poland are already involved in the ESPRIT and SMART studies; clinics in Estonia, Lithuania and Russia joined the SMART study in 2004 and are currently

working hard on study implementation. As this study is conducted on a global level, the contribution of East European countries is essential due to the large number of patients and to the large proportion of patients not previously exposed to antiretroviral therapy.

The Future

We are sure that collaborating will be of mutual benefit for CHIP and the clinics. First of all, HIV-clinicians in Eastern Europe will be part of a network of HIV-experts from across Europe, sharing experiences with colleagues and thus enabling optimal usage of antiretroviral drugs. Secondly, it will allow HIV-clinicians with relative little scientific experience to develop a scientific infrastructure within their clinics, thus enhancing the performance of other scientific projects. Finally, the collaboration may also help assure a more equal access to, and usage of antiretroviral therapy in the longer term.

Since late 2003, more extensive collaboration has been developed with individual clinics, and staff from CHIP has participated in meetings in Lithuania, Latvia, Belarus, Romania and Russia (Moscow) presenting new scientific results and discussing state-of-the-art management of HIV-patients. We are looking forward to further develop these collaborations in the coming years.

A special issue requiring collaboration is co-infection with HIV and mycobacterium tuberculosis. Even though this is an increasing problem in Eastern Europe where a special concern is the high prevalence of multi-drug resistance tuberculosis in the general population, only sparse data has been reported. We are currently developing plans for addressing this important clinical issue in a collaboration involving existing HIV-cohorts as well as tuberculosis clinics in Eastern Europe. The project is intended to start in 2005.

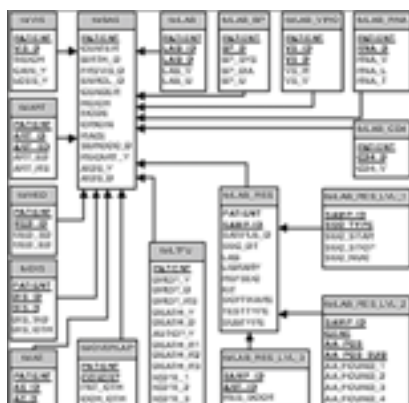
THE HICDEP PROJECT

HIV cohort studies have provided useful information on the natural history of HIV infection and the effects of antiretroviral therapy. It has become increasingly common to combine data from several cohorts into one dataset in order to address certain specific questions with more statistical power than can be achieved with the individual studies. This requires each cohort to map data into a standard format before merging. Until recently, this standard format has differed for each such collaborative analysis. To harmonise these formats the HIV Cohort Data Exchange Protocol (HICDEP) was developed, published and is freely available at CHIP. Once individual cohorts have set up means of transferring data into this format, as and when required, this should greatly facilitate data merging for future joint analyses.

HICDEP has been implemented in two collaborations:

1. The DAD study, which has recently decided to abandon the flat-file format and the data structure of the 5th data-merger in June 2004 for 11 cohorts. Approximately 35,000 patients will be based on the HICDEP tables and variables.
2. The EuroSIDA study, where some collaborating cohorts have started providing follow-up information according to HICDEP.

Other cohorts across the world have either applied the format for their collaborations or are using the format as the starting point for building new databases for their cohorts.



THE EUROVIR PROJECT

The understanding of the clinical implications of the development of mutations in the reverse transcriptase (RT) and protease (PR) genes of HIV associated with exposure to ART is incomplete. EuroSIDA has developed a resistance database to address this.

The data is derived from two sources:

1. Nucleotide sequences of both RT- and PR-encoding genes performed at the two central EuroSIDA virology laboratories (Badalona and Buckinghamshire)

From a total of 36,772 plasma samples collected in the EuroSIDA study, 3,048 have so far been selected for specific projects and sequenced at the two laboratories. Sequences for 2,442 plasma clinical isolates have been reported back to the EuroSIDA coordinating office from December 2002 to December 2004.

The process of: import, alignment against a reference sequence (HXB-2r) to identify differences from the reference sequence (mutations) and their output has been fully automated so that the output is ready for analysis by the statistical group.

These processes have been implemented into a set of tools that are currently being implemented as part of the UK HIV Resistance Database and the Statens Serum Institute as part of the Danish HIV Database.

2. Clinical virology reports from local laboratories used by clinicians to assess presence of genotypic resistance.

The data for this source have so far come from 1,074 clinical virology reports which have been collected and computerised. The reports originate from 14 different countries and are in just as many languages. For each type and version of the reports received, data entry is done after creating a template for the report; currently the database holds 54 different templates from 20 different laboratories. Each template consists of the complete setup of the report with predefined fields for mutations and interpretations of the resistance levels against a specific drug.

WORK PHILOSOPHY

WORK PHILOSOPHY

At CHIP we have felt a need to express a set of values for the work that we do. After several staff meetings, group discussions and careful deliberations by the management this has resulted in a set of values that all staff are dedicated to follow:



We dedicate ourselves to cultivate an open, positive attitude, to exhibit proactive behaviour and to deal with others in a respectful and empathic manner.



As a non-profit group we innovatively work for a global, common partnership and individual beneficial goals and development. This in order to answer the most important questions in the field of HIV related diseases by developing and conducting science of high quality.

We take responsibility for carrying out scientific projects through collaborative relationships for the common good.

This set of values will find their way into all aspects of the everyday work that we do, for the mutual benefit of CHIP, its partners and the scientific research.



ORGANISATION

Staff

The staff consist of scientific as well as administrative personnel; CHIP has 31 persons employed full-time and an additional 10 persons working part-time with data-entry .

A re-organisation of the staff took place in 2004 due to the increasing volume of activities and staff.

Most significant was the employment and appointment of a research manager and two study coordinators.

Clinical trials

A project coordinator, a statistician and a physician are responsible for the coordination of the clinical trials, in collaboration with the monitoring- and administrative staff in the group.

Cohort studies

All activities concerning the cohort studies are coordinated through a team consisting of a project coordinator, physicians, and a data manager. The group collaborates closely with the RFH (Royal Free Hospital, London, UK) statistical group.

Monitoring group

The monitoring group consists of a trained professional staff, most with a nursing background and additional GCP and protocol specific training. Each monitor is responsible for all activities at certain clinics in specific countries. This organisation has the advantage of each monitor being in direct contact with the site staff and can assist them on the various projects at their clinic as well as obtain specialised knowledge about implementing clinical trials in these countries. The general objective is to ensure trial implementation, training, on-going data validation as well as on-site source data validation.

Laboratory

Two technicians work in the laboratory - one is dedicated to research projects in collaboration with the department of infectious diseases, the other is dedicated to our plasma repository where an increasing number of plasma samples is received for short- and long-term storage.



General Office

Two assistants, both with MA degrees in languages and translation, assist monitors and physicians in coordinating efforts as well as do translations for the clinical trials.

The accounting group works under supervision of the finance department of the hospital and is responsible for the administration of the funding, including receiving and forwarding funding to participating clinics. Dedicated systems developers are responsible for database management and development of new approaches to data management.



Location

CHIP is primarily located in pavilion No. 1 - laboratory facility and freezer-bay is located within the main hospital complex, all at Hvidovre University Hospital, in Copenhagen, Denmark.

In addition, personnel are funded in collaborating groups:

- Statisticians working from Royal Free & University College Medical School, Department of Primary Care & Population Sciences, London, (UK)
- Monitors working from the Clinical Trials Unit (UASP), Hospital Clínic Barcelona, Spain
- Monitor working out of Zentrum der Inneren Medizin, J. W. Goethe University Hospital, Frankfurt, Germany.

Education

As an academic group affiliated with the University of Copenhagen, we have the responsibility to educate researchers. In the last year one physician have completed her Ph.D. programme and one physician have defended his doctoral thesis. Two new students for Ph.D. scholarships have been accepted

and we are currently investigating further expansion of this programme.

The European AIDS Clinical Society (EACS) aims at training younger European physicians in charge of HIV patient care through its EACS medical Exchange Programme for Young HIV Physicians. We participate in this programme together with the Department of Infectious Diseases at Hvidovre University Hospital as one of 10 European clinical centres.

We are constantly adding new staff to the group. Much time is spent on creating individualised training programmes for employees and ensuring that everybody at CHIP is continuously being updated.

The future

The group at CHIP continues to expand as new projects arise and more expertise is needed. As the number of projects to be coordinated is increasing, more staff will be needed in the future to meet these new challenges.

THESIS

CARDIOVASCULAR ADVERSE EFFECTS OF ANTIRETROVIRAL THERAPY

Summary of Ph.D. thesis defended successfully in November 2004

Nina Friis-Møller, MD

This thesis is based on work conducted in the period 2000-2003 during my employment as study coordinator for the D:A:D study at the Copenhagen HIV Programme, Hvidovre Hospital.

The purpose of the thesis was, based on data from the D:A:D study (the Data-collection on Adverse events of anti-HIV Drugs), a multinational cohort study of 23,468 HIV infected patients, to describe the prevalence of risk factors for cardiovascular disease in HIV infected patients, the possible association of antiretroviral therapy with such risk factors, and to examine a possible association between antiretroviral combination therapy and the risk of coronary heart disease.

The use of combination antiretroviral therapy for the treatment of HIV-infection has become abundant in the industrialized countries since it was introduced in the mid-1990ies. Several of the drugs can induce metabolic adverse effects, including a raise in cholesterol and triglycerides and the development of diabetes, which confers potential risk for cardiovascular disease.

There is a high prevalence of cardiovascular disease risk factors in HIV-infected individuals, both of such that can be associated to the antiretroviral therapy, and such that are unrelated (e.g. cigarette smoking). There is a clustering of risk factors among patients receiving regimens containing drugs from all three antiretroviral drug classes.

The HIV infected population is relatively young, 40 years on average, and the absolute risk of cardiovascular disease therefore relatively low (we observed an incidence of 3.5 per 1000 person-years of follow-up). We found that combination antiretroviral therapy was associated with a relative 26% increase in risk of myocardial infarction per year of exposure, and preliminary analyses suggest that this is largely mediated via metabolic changes. The observed risk was very similar to that predicted from the Framingham risk score, suggesting that such models can be applied in the setting of HIV infection and antiretroviral therapy, where the metabolic changes are partly or entirely medically induced.

These analyses are based on data from an observational study, why causality cannot be determined definitively. Nevertheless, the prospective study design, the extensive quality assurance measures, the carefully analysed data including multiple sensitivity analyses, the biological plausibility and confirmation from other studies comforts us on the reliability of the reported associations.

Additional follow-up is warranted before guidelines on possible medical intervention can be made, but based on the current evidence in this area clinicians are encouraged to carefully monitor the risk of cardiovascular disease in their patients receiving combination antiretroviral therapy, and to modify lifestyle risk factors where indicated.

DISSERTATION

PNEUMOCYSTIS JIROVECI

Applied molecular microbiology, epidemiology and diagnosis

Summary of doctoral dissertation defended successfully in May 2004

Jannik Helweg-Larsen, M.D.

P. jiroveci is an unusual fungal opportunist that remains a frequent cause of a severe pneumonia in immunocompromised patients, especially HIV patients, in which PCP remains one of the most common AIDS defining illnesses. *P. jiroveci* has been difficult to study, because the organism cannot be cultured in vitro and because only relatively small amounts of the organisms can be recovered from clinical samples. Many aspects of the infection are not fully understood. However, recent advances in DNA analysis have enabled the study of the infection. In the present studies PCR based methods, were used to investigate *P. jiroveci*.

Genetic variations in the internal transcribed spacer region (ITS) of the nuclear rRNA operon of *P. jiroveci* were found in samples from two presumed case-clusters of PCP (II) and a prospective cohort of HIV-positive patients with PCP (V). In the case-cluster study, we found no indication of a particular ITS type being responsible for either of the clusters. In the cohort study, we observed a complex picture of ITS types, with a high rate of different ITS genotypes and multiple genotypes in 23% of patients. A limited number of ITS sequence types accounted for the majority of types. These common types are not substantially different from sequence types reported from other countries, suggesting that *P. jiroveci* strains in Denmark are not unique. We found no specific temporal changes in occurrence of ITS genotypes, no evidence of clustering of specific genotypes, and no link between ITS genotypes and the severity of pneumonia, demographic variables or season of the year. To investigate the influence

of mixed infections and variability of genotypes we undertook a study of genotype heterogeneity in autopsy lungs (VI). We found that the infection is not clonal, that coinfections with multiple genotypes are common and that in some cases distinct populations of organisms may reside within the lung. Although these observations show that interpretation of genotype data should be cautious, the broad diversity of sequence types and the absence of temporal and clinical clusters of genotypes suggest that *P. jiroveci* may be ubiquitous, and that direct transmission from patient to patient may not be the predominant mode of infection.

The high sensitivity of PCR can be used to detect *P. jiroveci* DNA in upper respiratory samples. By using an improved single round PCR protocol we found that the PCR detection of *P. jiroveci* in oral wash samples had high sensitivity for diagnosing PCP patients among HIV-positive patients, but that some patients are PCR positive without evidence of clinical PCP (I). In a nested case-control study we detected *P. jiroveci* DNA by PCR in 4.4% of 367 patients with non-HIV associated pneumonia, and found that cases that were PCR positive were more sick from concomitant illness and had a higher rate of corticosteroid exposure (VII). Although carriage of *P. jiroveci* DNA was associated with a higher rate of mortality compared to controls, most of patients in whom *P. jiroveci* was detected never developed clinical PCP. Together with other reports, our findings suggest that while a negative PCR test has reasonable power to rule out PCP, a positive PCR test must be carefully interpreted in the context of clinical

findings. However, if properly used, PCR on oral washings is an easy, quick and sensitive method for the diagnosis of PCP, particularly in patients unwilling or unable to sustain BAL.

The described PCR method is now available as a routine test from Statens Serum Institute. In HIV-1 infected patients there has been concern if sulfa resistance might develop in *P. jiroveci*, following the widespread use of sulfonamides for prophylaxis and treatment of PCP. In the absence of a culture system, we searched for evidence of mutations in the dihydropteroate (DHPS) locus of *P. jiroveci*, the target of sulfone drugs (III). Among 152 episodes of AIDS associated PCP from 1989 to 1999 we found four different mutation patterns with non-synonymous nucleotide changes at codon 55, 57 and 60 of the DHPS locus.

A statistically significant increase in the rate of DHPS mutations was seen during the study period until 1996, followed by a decrease in 1997-1999 which correlated with changes in the rate of previous or current exposure to sulfonamide drugs. DHPS mutations were highly correlated to previous exposure to sulfa drugs and were associated with failure of sulfonamide prophylaxis. Mutations were also detected in patients without known exposure to sulfa drugs. After adjustment for other prognostic variables, presence of DHPS mutations remained an independent predictor of mortality. However, conflicting results from other studies have been published and presently it remains unclear whether the presence of *Pneumocystis* DHPS gene mutations confers clinical resistance to sulfa treatment. As

several patients with DHPS mutations have been successfully treated with high dose cotrimoxazole it is probable that DHPS mutations are indicators of low-level sulfa resistance which together with yet unknown sulfa resistance mechanisms may contribute to failure of sulfonamide treatment. Together these studies support a complex picture of transmission and infection of *P. jiroveci*. The infection is cleared after primary infection in childhood; however transient colonisation without clinical disease may happen. Although interpretation of genotype studies is difficult because infection is not clonal with some patients carrying more than one strain of *P. jiroveci*, there is so far little evidence that direct transmission of *P. jiroveci* is crucial for the risk of acquiring PCP. However, the finding that DHPS mutations are increasingly detected in patients without sulfa exposure suggests that indirect human transmission is nevertheless important.



PRESENTATIONS

11th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 2004

1. Predictors of Hypertension and Changes in Blood Pressure in HIV-infected Patients in the D:A:D study. R Thiebaut, W El-Sadr, N Friis-Møller, M Rickenbach, P Reiss, A D'Arminio Monforte, L Morfeldt, C Pradier, O Kirk, S De Wit, G Calvo, M Law, C Sabin, J D Lundgren and D:A:D Study Group. (DAD 75)
2. Final Week 48 Analysis of a Phase 4, Randomised, Open-label, Multi-center Trial to Evaluate Safety and Efficacy of Continued Lamivudine Twice Daily Versus Discontinuation of Lamivudine in HIV-1-infected Adults with Virological Failure on ongoing Combination Treatments Containing Lamivudine: The COLATE Trial. U Dragsted, Z Fox, L Mathiesen, C Katlama, M Youle, J Gerstoft, J N Bruun and J D Lundgren for the COLATE Trial Group. (COLATE 549)
3. Time to Triple Drug Class Failure after Initiation of HAART. A Mocroft, B Ledergerber, J P Viard, S Staszewski, M Murphy, A Chiesi, A Horban, A B Hansen, A N Phillips, J D Lundgren and the EuroSIDA Study Group. (EuroSIDA 554)
4. The Role of Genetic Polymorphisms of the MDR1 Gene in the MaxCmin1 Study. A Owen, Z Fox, L Almond, U Bak Dragsted, D Back, M Youle, J Lundgren, S Khoo, and the MaxCmin1 Steering Committee. (MaxCmin1 619b)
5. Lipid Profiles of Patients Enrolled in the MaxCmin2 Trial: A Randomised, Open-label Multi-centre Comparative Trial Evaluating the Safety and Efficacy of Lopinavir/ Ritonavir (400/100 mg twice daily) vs Saquinavir/Ritonavir SQV/r (1000/100 mg twice daily). S L Walmsley, J Benetucci, A Brutus, N Clumeck, U B Dragsted, B Gazzard, N Obel, P Vernazza, Z Fox, J D Lundgren and on behalf of the MaxCmin2 Trial Group. (MaxCmin2 720)
6. Cardio- and Cerebrovascular Events and Predicted Rates of Myocardial Infarction in the D:A:D study. M G Law, A D'Arminio Monforte, N Friis-Møller, R Weber, W El-Sadr, P Reiss, F Dabis, L Morfeldt, S De Wit, C Pradier, G Calvo, O Kirk, C Sabin, A N Phillips and J D Lundgren. (DAD 737)
7. Hepatitis B and Hepatitis C in the EuroSIDA Cohort: Prevalence and Effect on Mortality, AIDS Progression and Response to HAART. J Rockstroh, D Konopnicki, V Soriano, O Kirk, F Antunes, B Knysz, C Tural, S De Wit, A Mocroft, J Lundgren and the EuroSIDA Study Group. (EuroSIDA 799)

XV International AIDS Conference, July 2004, Bangkok

1. Predictors of the CD4 count response during the first 8 months of follow-up in the IL-2 arm of ESPRIT. K Ruxrungtham, Z V Fox, F Antunes, J D Bebhuck, R T Davey, B Gazzard, N G Klimas, A M Labriola, M H Losso, J D Neaton, S Staszewski, L Weiss, A N Phillips, J D Lundgren. (ESPRIT WeOrB1288)
2. Comparison of observed clinical event rates in the ESPRIT trial with projections from the EuroSIDA study. J D Lundgren, A Mocroft, J Bebhuck, S. Staszewski, F Antunes, B Knysz, M Law, A N Phillips, J Neaton. (ESPRIT/EuroSIDA WePeB5685)

44th ICAAC, October 2004, Washington

1. Comparison of 6 HIV-1 genotypic resistance algorithms for predicting viral load change to week 4. Z Fox, J Gerstoft, UB Dragsted, AN Phillips, P Cahn, J Gatell, JD Lundgren. (MaxCmin2 H-185)

6th International Conference on Adverse Drug Reactions and Lipodystrophy in HIV, October 2004, Washington

1. Association of risk toxicity with drug levels of saquinavir boosted with ritonavir in the MaxCmin 1 & 2 trials. JD Lundgren, Z Fox, US Justesen, S Warmsley, M Youle, P Vernazza, J Gerstoft, M Losso, and UB Dragsted on behalf of the MaxCmin trial groups. (MaxCmin 1&2 79)
2. Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen. A Mocroft, AN Phillips, V Soriano, J Rockstroh, A Blaxhult, C Katlama, A Boron-Kaczmarek, L Viksna, O Kirk, JD Lundgren for the EuroSIDA study group. (EuroSIDA 74)

7th International Congress on Drug Therapy in HIV Infection, November 2004 Glasgow

1. Interruption/stopping HAART and risk of clinical disease progression to AIDS/death in EuroSIDA. C Holkmann-Olsen, A Mocroft, S Vella, A Blaxhult, N Clumeck, O Kirk, M Fisher, C Katlama, A Phillips, J Lundgren (EuroSIDA P5)
2. What is the status of IL-2? J D Lundgren. (PL8.1)
3. Why do patients stop antiretrovirals used as part of an initial HAART regimen? Results from the EuroSIDA study group. A Mocroft, A Phillips, V Soriano, J Rockstroh, A Blaxhult, C Katlama, A Boron-Kaczmarek, L Viksna, O Kirk, J Lundgren (EuroSIDA PL14.1)
4. HIV-patients across Europe: regional differences in patient characteristics. D Podlekareva, W Bannister, L Viksna, A Mocroft, B Knysz, P Reiss, N Chentsova, D Duiculescu, JD Lundgren, O Kirk, The EuroSIDA Study. (EuroSIDA P67)

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1. **Changing incidence of CNS HIV-related diseases in the EuroSIDA cohort.** *d'Arminio Monforte A, Cinque P, Mocroft A, Goebel F-D, Antunes F, Katlama C, Justesen US, Vella S, Kirk O, Lundgren JD, for the EuroSIDA Study Group. Ann Neurol.* 2004; 55:320-328
2. **Lipid profiles in HIV-1-infected individuals receiving combination antiretroviral therapy: are different protease inhibitors or non-nucleoside reverse transcriptase inhibitors associated with different lipid profiles?** *Fontas E, van Leth F, Sabin CA, Friis-Møller N, Rickenbach M, d'Arminio Monforte A, Kirk O, Dupon M, Morfeldt L, Mateu S, Petoumenos K, El-Sadr W, de Wit S, Lundgren JD, Pradier C, Reiss P. J Infect Dis.* 2004;189
3. **Soluble urokinase receptor is elevated in cerebrospinal fluid from patients with purulent meningitis and is associated with fatal outcome.** *Ostergaard C, Benfield T, Lundgren JD and Eugen-Olsen J. Scand J Infect Dis.* 2004;36:14-19
4. **Clinical trial methodology and clinical cohorts: the importance of complete follow-up in trials evaluating the virological efficacy of anti-HIV medicines.** *Kirk O and Lundgren JD. Cur Opin Infect Dis.* 2004;17:33-37
5. **Indirect comparisons: a novel approach to assessing the effect of anti-HIV drugs.** *Lundgren JD, Phillips AN. BMJ.* 2004;328(7434):253
6. **The PLATO Collaboration. Predictors of CD4 count trend and mortality among HIV-1 - infected patients with virologic failure to all three antiretroviral drug classes.** *Writing committee: Ledergerber B, Lundgren JD, Walker AS, Sabin C, Justice A, Reiss P, Mussini C, Wit F, d'Arminio Monforte A, Weber R, Fusco G, Staszewski S, Law M, Hogg R, Lampe, Gill J, Castelli F, Phillips AN. Lancet.* 2004;364:51-62
7. **HIV survival benefit associated with earlier antiviral therapy.** *Mocroft A, Phillips AN, Lundgren JD. Ann Inter Med.* 2004;140(7):578-9
8. **Forscarnet used in salvage therapy of HIV-1 patients harbouring multiple nucleotide excision mutations.** *Mathiesen S, Roge BT, Weis N, Lundgren JD, Obel N, Gerstoft. AIDS* 2004;18(7):1076-78
9. **The Changing pattern of Kaposi's sarcoma in patients with HIV - 1994-2003.** *The EuroSIDA Study. Mocroft A, Kirk O, Clumeck N, Gargalianos P, Trocha H, Chentsova N, Antunes F, Stellbrink H-J, Phillips AN, Lundgren JD for the EuroSIDA study group. Cancer* 2004; 100:2644-2654
10. **Predictors of immunological failure after initial response to HAART in HIV-1 infected adults: a EuroSIDA study.** *Dragsted UB, Mocroft A, Vella S, Viard JP, Hansen AE, Panos G, Mercey D, Machala L, Horban A, and Lundgren JD; EuroSIDA study group. J Infect Dis.* 2004 Jul 1;190(1):148-55
11. **Reduktion af aids og dødsrater i EuroSIDA-studiet. Et observationsstudie.** *Kirk O, Mocroft A and Lundgren JD for the EuroSIDA study. Ugeskrift f Laeger.* 2004;166(26-31):2571-6
12. **HIV cohort collaborations: proposal for harmonization of data exchange.** *Kjaer J and Ledergerber B. Antivir. Ther.* 2004;9:631-3
13. **Nucleoside analogue use before and during highly active antiretroviral therapy and virus load rebound. Collaboration of HIV Cohorts:** *Phillips AN, Ledergerber B, Lundgren JD, Hogg B, d'Arminio Monforte A, Castelli f, Walker S, Staszewski S, Thiébaud R, Gazzard B, Saag M, Petoumenos K, Johnson M, Scullard G, Gill J, James I, Fisher M, Mussini C, Klein M, Costagliola D. J Infect Dis* 2004;190:675-87
14. **Retinal and extraocular cytomegalovirus end-organ disease in HIV-infected patients in Europe. A EuroSIDA study, 1994-2000.** *Yust I, Fox Z, Burke M, Johnson AM, Tuner D, Mocroft A, Katlama C, Ledergerber B, Reiss P, Kirk O, for the EuroSIDA study. Eur J Clin Microbiol Infect Dis.* 2004 Jul;23(7):550-9
15. **Rate of viral rebound according to specific drugs in the regimen in 2120 patients with HIV suppression.** *Phillips AN, Ledergerber B, Horban A, Reiss P, Chiesi A, Kirk O, Mulcahy F, Fisher M, Machala L, Lundgren JD; EuroSIDA Study Group. AIDS.* 2004 Sep 3;18(13):1795-804
16. **Cardio- and Cerebrovascular Events in HIV-Infected Persons. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group.** *Writing Committee: d'Arminio Monforte A, Sabin CA, Reiss P, Weber R, Kirk O, El-Sadr W, De Wit S, Mateu S, Petoumenos K, Dabis F, Pradier C, Morfeldt L, Phillips AN, Lundgren JD, and Friis-Møller N. AIDS* 2004, 18:1811-1817
17. **HIV remains a deadly disease.** *Lundgren JD HIV Med.* 2004;5:251-2
18. **Attenuation of the blood bacterial load by pre-treatment with G-CSF protects from fatal outcome and brain damage in Streptococcus pneumoniae meningitis in rats.** *Brandt CT, Lundgren JD, Lund SP, Frimodt-Møller N, Christensen T, Benfield T, Espersen F, Hougaard DM and Østergaard C. Infect Immun.* 2004 Aug;72(8):4647-53

19. **Starting antiretroviral therapy: why, when and response to HAART [review].** Mocroft A, Lundgren JD *J Antimicrob Chemother.* 2004 Jul;54(1):10-3. Epub 2004 May 26. Review
20. **Is the Salk principle still viable for the design of an effective HIV vaccine?** [editorial] *HIV Med.* 2004 Sep;5(5):315-6
21. **Current Epidemiology of Pneumocystis Pneumonia.** Morris A, Lundgren JD, Masur H, Walzer PD, Hanson D, Frederick T, Huang L, Beard C and Kaplan JE *Emerg Infect Dis.* 2004 Oct;10(10):1713-20
22. **Baseline Resistance and Virologic Outcome in Patients with Virologic Failure who start a Regimen Containing Abacavir: EuroSIDA Study.** Cabrera C, Cozzi-Lepri A, Phillips AN, Love-day C, Kirk O, Ait-Khaled M, Reiss P, Kjær J, Ledergerber B, Lundgren JD, Clotet B, Ruiz L on behalf of the EuroSIDA study group. *Antivir Ther.* 2004 Oct;9(5):787-800.
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Edited by: Kell E. Greibe, CHIP (Copenhagen HIV Programme)
Layout: Zofia Kruszona, AV-group, Hvidovre Hospital
Photo: Susanne Østergaard AV-group, Hvidovre Hospital
and Joachim Rode p. 2 portrait of Jens Lundgren.

Print: Kailow Graphic A/S
04/2005

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